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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/505,183	NEGISHI ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/2/07, 6/26/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8-17 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8-17 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The amendments received 2 April 2007 and 26 June 2007 have been entered. Claims 3-5, and 7 have been canceled. Claims 1, 2, 6, 8-17 have been amended in the submission of 2 April 2007 and the amendment made of record; claims 36-38 have been newly presented (2 April 2007) and made of record. Claims 1, 2, 6, and 37 have been amended in submission of 26 of June 2007 and the amendment made of record.

Claims 1, 2, 6, 8-17 and 36-38 are pending and under consideration in the instant application.

Information Disclosure Statement:

The Information Disclosure statement (IDS) submitted on 2 April 2007 has been considered. Signed copy is attached.

Withdrawn Objections/Rejections

Objections:

The objection to the information disclosure statement filed 18 August 2004 is withdrawn in view of submission of IDS on 2 April 2007.

Rejections:

The rejection of Claims 1-14 under 35 U.S.C. 101 as directed to non-statutory subject matter is withdrawn in view of applicant's amendment to the claims.

The rejection of Claim 1 under 35 U.S.C. 112, second paragraph as vague and indefinite in reciting the term "native" is withdrawn in view of applicant's amendment to the claims.

The rejection of Claim 1 under 35 U.S.C. 112, second paragraph as vague and indefinite in reciting "CAR" is withdrawn in view of applicant's amendment to the claims.

The rejection of Claims 2, 6 and 8 under 35 U.S.C. 112, second paragraph as vague and indefinite in reciting amino acid positions without presenting a reference sequence is withdrawn in view of applicant's amendment to the claims.

The rejection of Claim 6 under 35 U.S.C. 112, second paragraph as vague and indefinite for reciting "wherein the mutation corresponds to hCAR position Leu342 and hCAR position Leu343" is withdrawn in view of applicant's amendment to the claims.

The rejection of Claims 10 and 13 under 35 U.S.C. 112, second paragraph as vague and indefinite in reciting "confers" is withdrawn in view of applicant's amendment to the claims.

The rejection of Claim 16 under 35 U.S.C. 112, 2nd paragraph, is withdrawn in view of applicant's amendment to the claims.

The rejection of Claims 1, 2, 6, 8-17 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement and written description requirement is withdrawn in view of applicant's amendment to the claims. However, the amendments raise new issues under 35 U.S.C. 112, first paragraph which are set forth in detail below.

The rejection of Claims 1, 10-14, and 17 under 35 U.S.C. 102(b) as being anticipated by Kawamoto et al. (2000. Mol Endoc 14:1897-1905, cited on IDS of 18 August 2004) is withdrawn in view of applicant's amendment to the claims.

The rejection of Claims 1, 10-12, and 15-17 under 35 U.S.C. 102(a) as being anticipated by Tzammell et al. (2000. Mol. Cell Biol. 20:2951-2958) is withdrawn in view of applicant's amendment to the claims.

Maintained/ New Rejections

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 6, 8-17, and 36-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 6, and 37 are vague and indefinite in identifying the polypeptide of interest as a mutation of polypeptide sequence of GenBank Accession No. Z30425. The sequences identified by accession number are constantly being updated and changed; therefore the metes and bounds of the claims cannot be determined. It is suggested that claims be amended to read, for example, "the polypeptide of SEQ ID NO:18 (GenBank Accession No. Z30425)".

Claims 1 and 37 are vague and indefinite in reciting "a wild-type ....receptor...comprising one or more mutations...". It is unclear how a wild-type protein can comprise a mutation. Furthermore, the claims are vague and indefinite in reciting "one or more mutations..." without identifying an upper limit of the number of mutations encompassed by the claims. Therefore, the metes and bounds of the claims cannot be determined.

Claim 2 is vague and indefinite for reciting "wherein the one or more mutations corresponds to position Leu 342 and...position Leu343". It is unclear how the limitation of one or more mutations could require mutations at two residue positions.

Claim 16 is vague and indefinite in reciting "a CAR-responsive steroid.....". It is unclear how a steroid can be responsive to a receptor.

Claims 8-15, 17, 36 and 38 are included in this rejection as dependent upon rejected claims.

The rejection of Claims 1 and 9 as vague and indefinite for reciting "less constitutively active" (Claim 1) and "substantially decrease the non-constitutive activity" (Claim 9) is maintained for reasons of record and for reasons set forth below. Applicant traverses the rejection. The reason for the traversal is that the terms are defined in the specification. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

While the claims are to be interpreted in light of the teachings of the specification, it is improper to read limitations or embodiments of the specification into a claim (See MPEP 2111.01). The terms, as defined in the specification, are not limiting; thus the metes and bounds of the claim cannot be determined. A receptor that is constitutively active is one that initiates a signaling cascade in the absence of a cognate ligand; it is unclear how a receptor can be "more" or "less" constitutively active. The specification defines a less constitutively active receptor as any nuclear orphan receptor ... (or constitutive androstane receptor), that is not substantially constitutively active in vitro [paragraph 0033 of PGPUB 20050107590, the PGPUB of the instant invention]. Since "substantially" is a relative term, the definition in the specification is ambiguous. Furthermore, the specification goes on to teach "non-CAR has about 50% or less, 25% or less, 10% or less, 5% or less or 2% or less or even 0% constitutive activity as compared to CAR" [paragraph 0033]; this is a non limiting definition. Thus, one of ordinary skill in the art would be unable to determine whether a given mutated receptor meets the limitations of the claim.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9-17, and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide wherein the polypeptide comprises mutations at position Leu 342 or Leu 343 in a human polypeptide of SEQ ID NO:18, does not reasonably provide enablement for an isolated polypeptide wherein the amino acid sequence of the polypeptide comprises one or more mutations at any residue position in SEQ ID NO:18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are broadly drawn to a mutated human CAR protein comprising any mutation at one or more positions that renders the receptor non-constitutively active, that is responsive to xenochemicals and/or steroids. There is no upper limit to the number of mutations recited, nor an indication of which domains may be altered and which must be conserved.

The specification discloses: Examples of non-CAR sequences include, but are not limited to, CAR sequences having one or more mutations corresponding to hCAR position Leu 342 [paragraph 0034], a Leu 343 to Ala 343 (L343A) mutation, or both a L342A and a L343A mutation [paragraph 0086]. The specification teaches variants or fragments of SEQ ID NO:18 may also be encompassed by the limitations of the claims [paragraph 0076]. [0087]. Additionally, a non-CAR polypeptide can also include one or more conservative amino acid substitutions, as long as the polypeptide retains non-CAR biological activity [paragraph 0087]. The specification therefore provides several examples, but provides no further guidance as to which domains must be conserved and which are to be altered to obtain a receptor that has the new activity of being responsive to its cognate ligand.

Working examples: Example 7 teaches that an Ala substitution of Leu 342 of hCAR, as well as the double mutation L342A/L343A decreased hCAR constitutive activity. There are no examples, working or prophetic, of mutations at any other residue positions in the amino acid of SEQ ID NO:18 that results in a protein that no longer signals constitutively.

The state of the art discloses: The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain

functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, Merz et al., eds, Birkhauser, Boston, pp. 491-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data of the human CAR sequence of SEQ ID NO:18, and two examples of mutations which can be introduced and meet limitations of the claims to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions to arrive at the claimed invention, a receptor which is responsive to cognate ligands. Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which residues, other than 342 and 343, of SEQ ID NO:18 are to be mutated to obtain the required activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1, 9-17 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a polypeptide comprising one or more mutations of SEQ ID NO:18 wherein said mutations render the isolated polypeptide responsive to cognate ligands.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). These claims are drawn to a genus, i.e., polypeptides of SEQ ID NO:18, comprising one or more mutations, with no upper limit to the number of mutations.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

There are two species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* polypeptides comprising mutations at position Leu 342 or Leu 343. The disclosure of only two disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is polypeptides of SEQ ID NO:18, comprising one or more mutations, with no upper limit to the number of mutations.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claims 1, 2, 6, 8-14, and 17 under 35 U.S.C. 102(b) as being anticipated by Tomko et al. (1997. PNAS 94:3352-3356) is maintained for reasons of record and applied to newly submitted claims 37 and 38 for reasons of record and for reasons set forth below.

Applicant traverses the rejection. The reasons for the traversal are:

a. Tomko et al does not describe a sequence of a constitutively active nuclear orphan receptor and

b. The alignment of sequence taught by Tomko et al and the wild-type CAR receptor reference sequence provided in the instant specification and claims are highly divergent and have no sequence homology.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The sequence taught by Tomko et al is 99.4% identical to SEQ ID NO:18, the reference sequence recited in the claims of the instant invention (see enclosed alignment). Thus, in contrast to applicant's assertion, the sequence taught by Tomko exhibits an extremely high degree of identitiy to the sequence of the claimed invention (99.4%). The sequence taught by Tomko et al. differs from the reference sequence by two amino acids; the leu342 position of SEQ ID NO:18 is replaced by an alanine and the leu343 position of SEQ ID NO:18 is replaced by a proline. Thus, the sequence taught by Tomko et al differs from SEQ ID NO:18 by substitutions at the positions recited in claims 2, 6, 8, 37, and 38 and comprise a substitution of ala for leu at position 342, as required by claims 8, and 38. While Tomko et al does not teach the polypeptide as a mutation of SEQ ID NO:18, the polypeptide of Tomko et al meets all the limitations of claims 1, 2, 6, 8, 9, 17, 37 and 38 and thus, would be expected to meet all characteristics of the polypeptide of the claimed invention. Case law has established that a compound and all of its properties are inseparable, as are its processes and yields (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Thus, the polypeptide taught by Tomko et al also meets the limitations of claims 10-14. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or nonobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.)

Claims 1, 2, 6, 8-17 and 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Tomko et al. (1998. WO 98/33819). The reference teaches a sequence (see claim 3, page 67-68 and enclosed alignment) which is 99.4% identical to SEQ ID NO:18, the reference sequence recited in the claims of the instant invention. The sequence taught by Tomko et al. differs from the reference sequence by two amino acids; the leu342 position of SEQ ID NO:18 is replaced by an alanine and the leu343 position of SEQ ID NO:18 is replaced by a proline. Thus, the sequence taught by Tomko et al differs from SEQ ID NO:18 by substitutions at the positions recited in claims 2, 6, 8, 37, and 38 and comprise a substitution of ala for leu at position 342, as required by claims 8, and 38. The polypeptide has proline substituted for leucine at position 343, a conservative amino acid substitution, since both are nonpolar, hydrophobic residues, thus meeting the limitation of claim 9. Tomko et al. teaches the protein is substantially free of other proteins with which it is natively associated (page 7, 2nd paragraph), thus anticipating the limitations of claim 15. The reference teaches a pharmaceutical composition comprising the polypeptide (page 9, 1st paragraph), thereby anticipating the limitation of claims 17 and 36. The reference teaches detecting the presence or measuring the quantity of human CAR comprising contacting the biological sample with a binding partner capable of binding to the hCAR (page 7, last paragraph bridging page 8, 1st paragraph). The container or test tube comprising the binding partner and receptor used during the detection process could reasonably be interpreted to comprise a kit comprising the protein and steroid or xenochemical (binding partner); thus the reference anticipates the limitations of claim 16. While Tomko et al. do not explicitly teach a polypeptide wherein the polypeptide induces xenochemical metabolizing activity of a xenochemical-metabolizing enzyme, wherein the expression of the xenochemical metabolizing enzyme is regulated by an enhancer element, wherein the xenochemical-metabolizing enzyme metabolizes a xenochemical from the group consisting of phenobarbital or TCPOBOP, or wherein the polypeptide induces steroid metabolizing activity of a steroid metabolizing enzyme wherein the steroid-metabolizing enzyme metabolizes a steroid selected from the group consisting of estrogen and estradiol, case

law has established that a compound and all of its properties are inseparable, as are its processes and yields (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). Thus, the reference also anticipates the limitations of claims 10-14. Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on applicant to show a novel or nonobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Thus, the teachings of WO 98/33819 anticipate all the limitations of claims 1, 2, 6, 8-17 and 36-38.

Conclusion:

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS